Key factor discovered in the formation of metastases in melanoma

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Melanoma, the most aggressive of all skin cancer strains, is often fatal for patients due to the pronounced formation of metastases. Until now, a melanoma's rampant growth was mainly attributed to genetic causes, such as mutations in certain genes. However, researchers from the University of Zurich now reveal that so-called epigenetic factors play a role in the formation of metastases in malignant skin cancer. This opens up new possibilities for future cancer treatments.

Patients who visit the doctor because of malignant skin cancer often go too late - the aggressive cancer has already formed numerous metastases in their bodies. This rapid, malignant metastatic formation of melanoma, was previously put down to the high mutation rate that is characteristic of melanoma, i.e. genetic changes that stimulate the growth of cancer cells. Various cancer drugs therefore target the signaling pathways activated in the process, some of which have recorded astonishingly positive results in the clinic and are able to prolong the lives of seriously sick patients. Unfortunately, however, in most cases a kind of resistance develops: Eventually, the cancer cells no longer respond to the drug and the tumor spreads again. Evidently, the cancer cells have found new ways to grow. A team of researchers headed by Professor Lukas Sommer from the University of Zurich's Institute of Anatomy has now found a possible explanation for this dynamic behavior in cancer cells: The scientists believe that, depending on the prevalent conditions, cancer cells are able to "read" different genes and use them to their own end.

A highly active epigenetic factor in cancer cells

The readability of genes is controlled by epigenetic factors, namely factors which do not influence the gene sequence directly, but rather cause certain genes and chromosomal segments to be packed in different densities - and thus make them accessible for reading. Consequently, the Zurich-based researchers studied whether epigenetic factors are especially active in melanoma cells - and stumbled across EZH2, an epigenetic control protein found very frequently in malignant melanoma cells compared to normal cells.

Joining forces with dermatologists and oncologists from the University Hospital in Zurich and backed by the University Research Priority Program "Translational Cancer Research", Sommer's team was able to demonstrate that, in melanoma cells, the epigenetic factor EZH2 controls genes that govern tumor growth as well as genes that are important for the formation of metastases. In their study, the researcher exploited this central position of EZH2 to combat the cancer: They used a pharmacological inhibitor to suppress the activity of EZH2. As a result, the researchers were able to prevent the growth and malignant spread of the cancer in the animal model and human melanoma cells. "To our astonishment, we were able to use the approach to influence the progression of the disease, even if tumors had already developed," explains Sommer. Epigenetic factors like EZH2 therefore appear to be highly promising targets for future cancer treatments, especially combined with other drugs that are already available.

More information: Daniel Zingg, Julien Debbache, Simon M. Schaefer, Eylul Tuncer, Sandra C. Frommel, Phil Cheng, Natalia Arenas-Ramirez, Jessica Haeusel, Yudong Zhang, Michael T. McCabe, Caretha L. Creasy, Mitchell P. Levesque, Onur Boyman, Raffaella Santoro, Olga Shakhova, Reinhard Dummer, and Lukas Sommer. The epigenetic modifier EZH2 controls melanoma growth and metastasis through silencing of distinct tumour suppressors. *Nature Communications*, 22 January, 2015. DOI: NCOMMS7051

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